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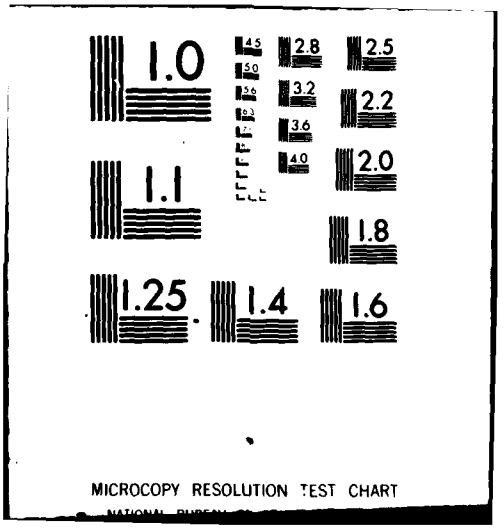
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THE EFFECTS OF ACUTE ALTERATIONS IN HEMODYNAMICS, OXYGEN AVAILABILITY AND ACID-BASE BALANCE ON THE PERMEABILITY OF THE GASTRIC MUCOSA

ANNUAL PROGRESS REPORT
(FOR THE PERIOD 1 OCT. 78 to 30 SEPT. 79)

DATE OF REPORT MARCH 1980

BY

WALLACE P. RITCHIE, JR., M.D.

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20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*
Using a previously described model for acute gastric mucosal ulcerogenesis, developed under the auspices of the current contract ~~(Gastroent. 68:699, 1975)~~, studies from this laboratory during the period covered by this progress report indicate (1) that, in the face of an imposed topical acid load, H_1 and H_2 receptor blockade, either alone or in combination, effects no change in gastric mucosal permeability to cations or in mucosal blood flow and affords no protection against bile acid-ischemia induced ulcerogenesis; (2) that the addition of exogenous histamine neither protects nor augments lesion formation under

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these circumstances; (3) that the dihydroxy secondary bile acids are more damaging to gastric mucosa than are the trihydroxy primary bile acids; and (4) that in non-ischemic bile acid-treated gastric mucosa, mucosal blood flow increases in proportion to the magnitude of H "back-diffusion" induced, a response not mediated by histamine receptors.

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The Effects of Acute Alterations in Hemodynamics, Oxygen Availability, and Acid-Base Balance on the Permeability of the Gastric Mucosa.

II. PRINCIPAL INVESTIGATOR:

Wallace P. Ritchie, Jr., M.D., Ph.D.
Department of Surgery
University of Virginia School of Medicine
Charlottesville, Virginia 22908
472-36-6392

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IV. PROGRESS REPORT:

(1) Effect of H_1 and H_2 receptor blockade on gastric mucosal permeability to cations and bile acid-induced ulcerogenesis. Recent reports suggest that, in the presence of topical acid, combined H_1 and H_2 receptor blockade decreases gastric mucosal permeability and H_2 blockade alone ameliorates bile-acid-induced "stress ulcer". The present study was undertaken to re-examine these assertions using the sensitive model outlined. Ex-vivo chambered wedges of mucosa were prepared in four groups of animals, each of which was studied during nine sequential 15 minute periods. Group A mucosa were exposed, during 1-3, to topical acid test solution alone (ATS), during 4-6, to ATS+ 2mM Na taurocholate (TC), and during 7-9 to ATS+TC+wedge-specific vasopressin (VP), $5x10^{-3}$U/Kg-min. Groups B, C, and D were treated analogously except that group B was pretreated with cimetidine, 300mgm IV, group C with pyribenzamine, 10mgm/Kg IM, and group D, with both. The dose of cimetidine employed has been shown to produce significant inhibition of histamine stimulated gastric acid production in this model for a time period comparable to that of the current experiment. The dose of the H_1 receptor blocking agent was precisely the same as that reported to reduce, in combination with cimetidine, mucosal permeability to cations.

The parameters evaluated included (1) net flux of H+ and Na+ (μEq); (2) the potential difference (mV); (3) aminopyrine clearance (ml/min); and (4) the lesion index, graded 0-5. The results per 15 minutes (±SEM) indicate that, in mucosa exposed to ATS, ΔH+= -43±12, ΔNa+ = +133±13, PD=-63±1, AC:2.3±0.4, and LI=O. During ATS+TC, ΔH+ = -219±21, ΔNa + = +206±17, PD = -45±1, AC = 2.8±0.5, and LI=O. H_1, H_2 and H_1 + H_2 blockade effected no significant change under either circumstance. In bile acid treated ischemia mucosa:

GROUP	ΔH+	ΔNa+	$\overline{PD}$	AC	LI
Control (n=7)	-233±20	+323±20	-24±1	1.1±0.1	3.3±0.4
H_1 (n=6)	-233±27	+333±24	-20±2	0.9±0.2	3.7±0.2
H_2 (n=5)	-266±32	+361±22	-24±1	1.2±0.1	3.2±0.4
H_1+H_2 (n=6)	-277±24	+324±17	-21±1	1.0±0.1	3.5±0.2

Thus, in the face of an imposed topical acid load, H_1 and H_2 blockade, both alone and in combination, effects no change in gastric mucosal permeability to cations or blood flow and affords no prc ction against bile acid-induced lesion formation.

(2) Effect of histamine stimulation on the magnitude of acute gastric mucosal damage induced by bile acids and ischemia.
It has been demonstrated in-vitro that burimamide-inhibited amphibian gastric mucosa is less resistant to bile acid induced damage, as judged by electrical indicies, than is spontaneously secreting mucosa. The present study used ex-vivo vascularized chambered wedges of proximal canine mucosa to examine the converse: the potential protective effect of active H+ secretion induced by histamine on acute mucosal ulcerogenesis caused by the topical application of Na taurocholate in acid solution and concomitant pharmacologic ischemia. Methods: Groups of dogs (n= 5-6ea) were studied during 3 consecutive 30 minute periods. Group A= topical acid test solution (ATS) during periods (1), (2), (3). Group B= (1) ATS, (2) ATS, (3) ATS+vasopressin (VP), 0.1×10^{-2}U/Kg-min delivered via the splenic artery. Group C= (1) ATS, (2) ATS+H+TC, (3) ATS+H+TC+ VP. Parameters evaluated during each period=net H+ flux, aminopyrine clearance, and lesion index, graded 0-5. Results: In the absence of VP, TC significantly increased net H+ loss and AC relative to ATS; H resulted in significnat H+ gain and further increased AC relative to ATS+TC; no lesions were noted under any circumstance. The results observed during period 3 (±SEM/30min):

	ATS	ATS+VP	ATS+TC+VP	ATS+H+TC+VP
ΔH+ (μEq)	-109±43*	-108±60*	-242±53	-55±57*
AC (ml/min)	1.57±0.27	0.70±0.16*	1.13±0.27	1.57±0.49
LI (0-5)	0*	0.3±0.2*	2.4±0.3	1.6±0.5

*Significant difference vs. ATS+TC+VP.

Thus, the combination of topical bile acid in acid solution and relative mucosal ischemia (compared to ATS+TC, where AC=3.36±0.69ml/min) is acutely ulcerogenic. Concomitant histamine infusion neither protects nor augments lesion formation under these experimental conditions.

(3) Mediators of Bile Acid-Induced Enhancement of Gastric Mucosal Blood Flow. The topical application of bile acid in acid solution to non-ischemic gastric mucosa (GM) increases mucosal blood flow (MBF), an important cytoprotective phenomenon since, when it alone is blunted, mucosal ulcerogenesis results. The present study addressed the hypothesis that the magnitude of this response is related to the absolute amount of H+ "back diffusion" induced and that endogenous histamine release is the intramucosal mediator. Using vascularized chambered ex-vivo wedges of GM, 3 groups of dogs were studied during 3 sequential 30 minute periods. Group A (n=6): topical neutral test

solution (NTS; pH=7.0) during 1, NTS+2.5 mM sodium taurocholate (TC) during 2, and during 3, NTS+5 mM TC. Group B (n=11): topical acid test solution (ATS=100 mM HCl) during 1, ATS=2.5 TC during 2, and ATS=5 TC during 3. Group C(n=7) was treated in the same manner as group B except that each dog was pretreated with the H_1 and H_2 blockers, pyribenzamine (10 mg/Kg IM), and cimetidine (300 mg IV). Parameters evaluated: (1) net flux H+, Na+ (ΔH+, ΔNa+), (2) MBF, determine by radiolabelled microsphere embolization, (3) potential difference (PD). Results (±SEM)/30 minutes:

	NTS	ATS	NTS	ATS	NTS	ATS
ΔH+ (μEq)	0	-96±22*	0	-405±40*+	0	-683±37*+
PD (mV)	-59±2	-62±1	-53±2*	-47±1*+	-45±2*	-38±1*+
MBF(ml/min)	4.7±0.8	6.0±0.7	4.4±0.8	8.4±1.0*+	4.2±1.0	10.4±1.0*+

*Significant difference vs NTS; + Significant difference vs 0 nM TC, same group.

The addition of blockers effected no change from ATS alone in any parameter at any (TC) except at 5 TC, where MBF increased (to 15.8± 2.6 ml/min.). CONCLUSIONS: (1) In non-ischemic GM, MBF increases in the presence of greater than normal ΔH+. (2) The amplitude of this response is dependent on the absolute magnitude of the increase in H+ "back diffusion" observed ($p<0.01$). (3) Enhanced MBF is not mediated by H_1 and H_2 receptor related histamine release. In fact, receptor blockage augments the response at 5mM TC.

(4) Ulcerogenic Potential of Primary vs. Secondary Bile Acids in Gastric Mucosa. Although the secondary (2^o) bile acids are more damaging to colonic mucosa than are the primary (1^o) bile acids, the existence of a similar circumstance in gastric mucosa has been inadequately documented. The present study addressed this problem by comparing the effect of an identical (and physiologic) concentration of the 2^o BA, taurodeoxycholic a. (TDC) to its parent 1^o BA taurocholic a. (TC) in both ischemic and non-ischemic GM. METHODS: Using chamber ex-vivo wedges of proximal GM, 2 groups of dogs were studied during 9 sequential 15 minute periods. Group A (4 dogs)=topical acid test solution alone (ATS=100mM HCl) during periods 1-3; ATS+1mM TC during 4-6; and, during 7-9, ATS+1mM TC+vasopressin (VP=$5x10^{-3}$U/Kg-min) infused into the splenic artery. Group B (4 dogs)were similarly treated except that the BA employed was TDC. Parameters evaluated=(1) net flux H+, Na+ (ΔH+, ΔNa+), (2) potential difference (PD), (3) mucosal blood flow (MBF), determined by radiolabeled microsphere embolization, and (4) the lesion index (LI), graded 0-5 by an independent observer using photographs. RESULTS (±SEM)/15 minutes:

	ATS (1-3)		ATS+1mM BA(4-6)		ATS+1mM BA+VP(7-9)	
GROUP	A	B	A	B	A	B
PD (mV)	-64±1	-63±1	-60±1+	-48±1+*	-41±1+	-28±1+*
ΔH+ (μEq)	-8±15	-1±18	-97±13+	-157±20+*	-105±21+	-250±30*+
MBF(ml/min)	11.2±2.0	12.0±2.5	9.0±1.4	13.6±4.8	2.5±0.7+	2.9±0.5+
LI(0-5)	0	0	0	0	0.9±0.4+	2.6±0.4+

+P 0.05 vs. ATS, same group; *p 0.025 vs. A(TC)

Thus, at an identical (and physiologic) concentration, 2^{o} BA induce a greater depression on PD, a more profound increase in mucosal permeability to H+, and in ischemic GM, a more severe degree of gross mucosal damage than do 1^{o} BA. CONCLUSION: 2^{o} BA are more damaging to GM than are 1^{o} BA, an effect undoubtedly related to their greater lipid solubility and consequent capacity to disrupt cell membranes.

V. PUBLICATIONS DURING THE CONTRACT YEAR:

1. Ritchie, W.P., Jr. and Cherry, K.J., Jr.: Influence of $[H^{+}]$ on Bile Acid Induced Acute Gastric Mucosal Ulcerogenesis. Ann. Surg. 189:637-642, 1979.

2. Ritchie, W.P., Jr. and McRae, D.B., Jr.: Effect of H_1 and H_2 Receptor Blockade on Gastric Mucosal Permeability to Cations and Bile Acid Induced Ulcerogenesis. Gastroent. 76:1227, 1979. Abstract.

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4. Ritchie, W.P., Jr.: Invited Commentary on "Restraint Induced Stress Ulcer. Parts I and II." World Journal of Surgery 4:101-103, 1980.

5. Felger, T.S., and Ritchie, W.P., Jr.: Ulcerogenic Potential of 1^{o} vs. 2^{o} Bile Acids in Gastric Mucosa. Surgical Forum 30:324-326, 1979.

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